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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,842	11/17/2000	Roger Briesewitz	STAN-131	8224

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,842	BRIESEWITZ ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18,22-26,30-34,36 and 39-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18, 22-26, 30-34, 36, and 39-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 16-18, 22-26, 30-34, 36, and 39-56 are pending.

2. In view of the amendment filed 8/19/05, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 16-18, 22-26, 30-34, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for directing the biodistribution of a drug that binds to a protein target, wherein the drug is directed to an intracellular space upon administration to a mammalian host, said method comprising: administering to said host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety and a targeting moiety that binds to an intracellular biodistribution modulating protein optionally joined by a linking group, wherein said targeting moiety is a peptidyl-prolyl isomerase ligand for FKBP or cyclophilin selected from the group consisting of FK506, rapamycin and cyclophilin, said bifunctional molecule exhibits a modulated biodistribution upon administration to said host as compared to a free drug control, and to direct the biodistribution of said drug to an intracellular space as compared to a free drug control, (2) the said method wherein the bifunctional molecule exhibits enhanced efficacy and reduced toxicity upon administration to said host. (3) The said method wherein the bifunctional molecule further comprises a linking group, (4) The said method wherein the bifunctional molecule does not include a linking group, (5) the said method wherein the bifunctional molecule is administered as a pharmaceutical preparation, (6) the said method wherein the host is a mammalian host such as human, **does not** reasonably provide enablement for a method as set forth in claims 16-18, 22-26, 30-34, and 36 wherein the targeting moiety of the bifunctional molecule is any molecule that has an affinity for its intracellular biodistribution modulating protein of merely at least about 10^{-4} M that binds to any intracellular biodistribution modulating protein, and wherein the drug moiety of the bifunctional molecule, any bifunctional molecule having a molecule weight that does not exceed about 5000 daltons consisting of any drug moiety, any drug moiety is any small molecule,

optionally joined by a linking group to any intracellular biodistribution molecule for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only bifunctional molecule having a drug of interest such as doxorubicin, methotrexate, vincristine, etoposide covalently linked through a targeting moiety such as FK506 or rapamycin that binds to an intracellular biodistribution modulating protein such as FKBP as a method for directing the biodistribution of a drug upon administering to a host.

The specification does not teach how to make all bifunctional molecules for the method as set forth in claims 16-18, 22-26, 30-34, and 36 for the following reasons: The claimed method in claims 16-18, 22-23, 30-34, and 36 encompasses all bifunctional molecules having a molecule weight that does not exceed about 5000 daltons comprising any targeting moiety optionally joined to any drug moiety such as any active drug derivative, and any small molecule. The claimed method in claims 24-26 encompasses all bifunctional molecules consisting of *any* targeting moiety optionally joined by a linking group to any drug moiety such as any active drug derivative, and any small molecule wherein said targeting moiety has an affinity for its intracellular protein of merely at least "*about* 10^{-6} M".

There is insufficient guidance as to the structure of *all* "targeting molecule" of the bifunctional molecule that binds to all "intracellular biodistribution modulating protein", and all "drug active derivative thereof" and "small molecule" of the bifunctional molecule for the claimed method without the amino acid sequence, let alone how to make all the targeting molecule for the claimed method. It is known that not all drug targeting to intracellular space is effective for treating all disease. Further, there is insufficient guidance as to which undisclosed "small molecule", and "derivative" of which drug is effective for targeting to which intracellular

space when optionally joined by a linking group to any targeting moiety that binds to all intracellular biodistribution modulating protein.

Stryer *et al,* of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Without the specific amino acid sequence of any drug, and active derivative thereof, and any targeting moiety, one skill in the art cannot make, much less use the claimed method.

Briesewitz *et al,* of record, teach that in general, the creation of unfavorable contacts in a bifunctional molecule that binds to intracellular protein target is far easier to achieve than favorable contacts due to steric hindrance and/or electrostatic repulsion (See page 1956, column 2, in particular). Given the unlimited number of undisclosed targeting moiety, either linked or not linked to any drug derivative and any small molecule in the bifunctional molecule for the claimed method, it is unpredictable which undisclosed targeting moiety is effective for which undisclosed small molecule and drug derivative in the bifunctional molecule having a molecular weight that does not exceeds about 5000 daltons, in turn, would be useful for the claimed method for directing the biodistribution of any drug that binds to any undisclosed protein target as a pharmaceutical preparation.

Further, Rihova et al teach the fate of the drug conjugate depends on a number of factors such as the target antigen, the targeting ligand within the cell type, the affinity of interaction, the rate of internalization, the rate of degradation, intracellular routing and the type of drug for the particular disease (see page 277, in particular). The term "about" broadening the affinity to as low as 10^{-5} M. Given such low affinity of the claimed targeting moiety for its intracellular protein in the claimed method, the binding specificity of the targeting molecule is non-specific at best. Further, there is a lack of in vivo working example demonstrating such bifunctional molecule is of any use, much less for treating any disease.

With regard to linker, Rihova et al teach drug such as doxorubicin has be released from its carrier in order to be pharmacologically active. A non-degradable linker such as Gly-Gly is inactive (see page 283, col. 2, second full paragraph, in particular). Given the unlimited number

of drug, small molecule and derivative linked to unlimited number of targeting molecule with low affinity via unspecified linker, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 8/19/05 have been fully considered but are not found persuasive.

Applicants' position is that the claims are not directed to all possible targeting molecules but specifically those targeting molecules that (1) when in complex with a drug moiety with or without an optional linker moiety, the complex as a whole does not exceed 5000 daltons, and (2) have an affinity for their intracellular protein of at least about 10^{-6} M (size and affinity). The specification provides extensive description of the bifunctional molecules employed in the subject methods, description of each of the component parts of the molecule, e.g. drug moieties (see page 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23). The specification teaches how to make the targeted bifunctional molecules (pages 24 to 28), guidance on how to screen candidate bifunctional molecules for suitability of use in the claimed method is provided on page 25. While such screening does involve experimentation, it is not undue. Respect to treatment and disease, the claims of the specification do not require a therapeutic result be achieved.

In response, the specification merely extends an invitation to one skill in the art to come up with the claimed bifunctional molecule without the chemical structure. There is insufficient guidance as to the structure of *all* "targeting molecule" of the bifunctional molecule that binds to all "intracellular biodistribution modulating protein", and all "drug active derivative thereof" and "small molecule" of the bifunctional molecule for the claimed method without the amino acid sequence, let alone how to make all the targeting molecule for the claimed method. It is known that not all drug targeting to intracellular space is effective for treating all disease. Further, there is insufficient guidance as to which undisclosed "small molecule", and "derivative" of which drug

is effective for targeting to which intracellular space when optionally joined by a linking group to any targeting moiety that binds to all intracellular biodistribution modulating protein.

Stryer *et al,* of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Without the specific amino acid sequence of any drug, and active derivative thereof, and any targeting moiety, one skill in the art cannot make, much less use the claimed method.

Briesewitz *et al,* of record, teach that in general, the creation of unfavorable contacts in a bifunctional molecule that binds to intracellular protein target is far easier to achieve than favorable contacts due to steric hindrance and/or electrostatic repulsion (See page 1956, column 2, in particular). Given the unlimited number of undisclosed targeting moiety, either linked or not linked to any drug derivative and any small molecule in the bifunctional molecule for the claimed method, it is unpredictable which undisclosed targeting moiety is effective for which undisclosed small molecule and drug derivative in the bifunctional molecule having a molecular weight that does not exceeds about 5000 daltons, in turn, would be useful for the claimed method for directing the biodistribution of any drug that binds to any undisclosed protein target as a pharmaceutical preparation.

With respect to the argument that the specification on page 25 discloses "typically, the screening assay will involve observing the biodistribution of the bifunctional molecule and comparing to a free drug control, e.g. suitable animal model, this is merely an observation for drug distribution. It is not a binding assay where it will enable one skill in the art to screen for the targeting moiety that binds to a particular protein target, in turn, would be useful for making the bifunctional molecule in the claimed method.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 24 and 26 stand rejected under 35 U.S.C. 102(b) as being anticipated by Forsgren et al (Cancer Res 39(12): 5155-64, Dec 1979; PTO 892) as evident by Asai et al (Acta Endocrinol (Copenh) 87(1): 173-80, Jan 1978; PTO 892).

Forsgren et al teach a method of targeting a drug to an intracellular site of a mammalian host such as male rat wherein the method comprises administering to the rat a bifunctional molecule such as Estracyt which consisting of a drug moiety such as nitrogen mustard linked to a targeting moiety such as estradiol-17 beta phosphate. The dephosphorylated metabolite of estracyt is estramustine that has affinity for its intracellular protein such as soluble estramustine binding protein of 10 to 30 x 10^{-9} M which is "at least" 10^{-6} M (see abstract, in particular). The reference bifunctional molecule exhibits a modulate biodistribution to the ventral prostate gland upon administration to a mammalian host (see abstract, in particular). As evident by the evidentiary reference, Asai et al teach the estradiol moiety in the Estracyt conjugate is useful as a carrier for selective distribution of the compound to the tissues (see abstract, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/19/05 have been fully considered but are not found persuasive.

Applicants' position is that claims 24 and 26 are directed to methods for modulating biodistribution of a drug to an intracellular space in a host wherein both of drug moiety and the targeting moiety bind to intracellular proteins. In other words, the drug moiety and the targeting moiety bind to proteins that exist within a cell. Forsgren discloses the binding characteristics of a rat protein that binds estramustine phosphate. The reference binding protein for estramustine is a secretory protein, not an intracellular protein target.

In response, Forsgren et al teach a method of targeting a drug to an intracellular site of a mammalian host such as male rat wherein the method comprises administering to the rat a bifunctional molecule such as Estracyt which consisting of a drug moiety such as nitrogen mustard linked to a targeting moiety such as estradiol-17 beta phosphate. The dephosphorylated metabolite of estracyt is estramustine that has affinity for its intracellular protein such as soluble estramustine binding protein of 10 to 30 x 10^{-9} M which is "at least" 10^{-6} M (see abstract, in particular). As evidence by the teachings of Asai et al that the estradiol moiety in the Estracyt conjugate is useful as a carrier for selective distribution of the compound to the tissues (see abstract, in particular).

With respect to the argument that estramustine binding protein is a not an intracellular protein target, the estrmustine binding protein is a cytosolic protein that is located within cytoplasm of a cell (intracellular space) (see abstract of Forgren et al, in particular). Therefore, the reference cytosolic protein (estramustine binding protein) is still an intracellular protein since it is within cytoplasm of the cell.

7. Claims 16-18, 22-26, 30-34, and 36 stand rejected under 35 U.S.C. 102(b) as being anticipated by Szepeshazi et al (Anticancer Drugs 8(10): 974-87, November 1997; PTO 892) as evident by Nagy et al (Proc Natl Acad Sci USA 93: 2464-2469, March 1996; PTO 892) and Nagy et al (Proc Natl Acad Sci USA 93: 7269-7273, July, 1996: PTO 892).

Szepeshazi *et al* teach a method for directing the biodistribution of a drug that binds to a protein target by administering to a mammalian host such as a mouse an effective amount of various bifunctional molecules such as AN-207 and AN-152 consisting of a drug moiety such as a small molecule doxorubicin or an active derivative thereof such as 2-pyrrolino-Doxorubicin and a targeting moiety such as LH-RH analogs that binds to an intracellular biodistribution modulating protein such as LHRH receptors that are located intracellular space (See entire document, abstract, in particular). The reference bifunctional molecule modulates the biodistribution of the doxorubicin to the site of LHRH receptor expressing tumor cells upon administration to the mouse as compared to free drug control and thereby enhances the efficacy of the drug by decreasing cell proliferation and inducing apoptosis of tumor cells (See col. 1, page 975, in particular). The reference drug binds to a protein target such as topoisomerase I and II (See page 985, col. 1, second paragraph, in particular). The reference AN-201 inherently has a molecular weight of 2029.57 daltons as evident by the teachings of Nagy et al who shows that 2-pyrrolino-Doxorubicin has a molecular weight of 595 daltons (See Figure 2, in Proc Natl Acad Sci USA 93: 2464-2469, March 1996) and LH-RH targeting moiety has a molecular weight of 1434.57 daltons (See pGlu-His-Tryp-Ser-Tyr-D-*Lys*-Leu-Arg-Pro-Gly of Figure 1 on page 7271 of Nagy et al in Proc Natl Acad Sci USA 93: 7269-7273, July, 1996; PTO 892). The molecular weight of the targeting molecule can be calculated by adding the molecular weight of 2-pyrrolino-Doxorubicin and the molecular weight of pGlu-His-Tryp-Ser-Tyr-Lys-Leu-Arg-Pro-Gly which, in turn, can be calculated by adding the molecular weight of each amino acids such as Glu has a molecular weight of 147.13, His has a molecular weight of 155.16, Trp has a molecular weight of 204.23, Ser has a molecular weight of 105.09, Tyr has a molecular weight of 181.19, Lys has a

molecular weight of 146.19, Leu has a molecular weight of 131.18, Arg has a molecular weight of 174.20, Pro has a molecular weight of 115.13 and Gly has a molecular weight of 75.07). Thus the reference bifunctional molecule has a molecular weight of 2029.57 daltons, which does not exceed the claimed about 5000 Daltons. The reference bifunctional molecule comprises a glutaric acid spacer (See Figure 1 on page 7271, Nagy et al (Proc Natl Acad Sci USA 93: 7269-7273, July 1996; PTO 892). The reference bifunctional molecule can also be formed without a linking group by covalently linking the drug moiety via ε amino group of its D-Lys of the targeting molecule LH-RH as evident by the teachings of Nagy et al (See Figure 1 on page 7271, Nagy et al (Proc Natl Acad Sci USA 93: 7269-7273, July, 1996; PTO 892). The reference bifunctional molecules AN-207 and AN-152 exhibit reduced toxicity and enhanced efficacy upon administering to the host (See entire document, abstract, in particular). Nagy et al further teach that drug targeting is a modern approach that is being tried to overcome the problem of nonselective toxic effects of systemic chemotherapy (See page 7271, col. 2, in particular) and 2-pyrrolino-Dox bifunctional molecule is 500-1000 times more active than its parent compound (Dox) (See page 7272, col. 2, 1st paragraph, in particular) and much less toxic in vivo (see page 7272, col. 2, last paragraph, in particular). Claim 32 is included in this rejection because the reference bifunctional molecules are intended to treat human having mammary cancers that have LH-RH receptors as taught by Szepeshazi (See abstract, in particular) and Nagy et al (see abstract of PNAS vol 93: 2464-1569, 1996, in particular). Claim 36 is included in this rejection because the reference endogenous biodistribution modulating protein such as LH-RH receptor is internalized after ligand binding. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/19/05 have been fully considered but are not found persuasive. Applicants' position is that methods for modulating biodistribution of a drug to an intracellular space in a host wherein both of drug moiety and the targeting moiety bind to intracellular proteins. In other words, the drug moiety and the targeting moiety bind to proteins that exist within a cell. In contrast, Szepeshazi et al discloses a series of compounds comprising doxorobubicin and luteinizing hormone releasing hormone (LH-RH) wherein the compounds are targeted to the LH-RH cell surface receptor. The Office Action incorrectly characterizes the LH-RH receptors as being located in the intracellular space; however, LH-RH receptors are located on the cell membrane in the extracellular space (e.g., outside of the cell), not the intracellular space – inside the cell (see discussion of LH-RH receptor levels beginning in col. 2, page 980).

In response, high affinity LH-RH receptor is located in the nuclear, perinuclear and cytoplasm of cancer cells and only the low affinity LH-RH is located in the membrane as evidence by the enclosed journal paper Szende et al (Proc Natl. Acad Sci USA Vol 88: 4153-56, 1991; PTO 892). Szende et al teach luteinizing hormone releasing hormone receptor is located in the nucleus and the cytoplasm and only low affinity receptors for LH-RH are found on the membrane using immunogold labeling method (see Fig. 1, page 4155, col. 2, in particular). This is consistent with the findings of Szepesbazi et al that there are two classes of LH-RH receptors in 52% human breast cancers (see page 985, col. 1, last paragraph, in particular) and LH-RH receptor levels on tumor membranes were not detectable after treatment with the reference LH-RH agonist (see page 985, last paragraph, in particular). Szepeshazi et al further teach hormones and growth factors may be used as delivery molecules to deliver toxic molecules to cancer cells (see page 983, col. 1, first paragraph, in particular).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 24-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Forsgren et al (Cancer Res 39(12): 5155-64, Dec 1979; PTO 892) as evident by Asai et al (Acta Endocrinol (Copenh) 87(1): 173-80, Jan 1978; PTO 892) in view of Trouet et al (Proc Natl Acad Sci USA 79: 626-629, Jan 1982; PTO 892).

The teachings of Forsgren et al as evident by Asai et al have been discussed supra.

The invention in claim 25 differs from the teachings of the references only in that the method wherein the bifunctional molecule comprises a linking group.

Trouet et al a method of covalent linkage between a drug moiety such as dauxorubicin (DNR) and any targeting moiety via a linking group such as Leu-Ala-Leu or Ala-Leu-Ala-Leu (see page 628, Table 1, Figure 1, in particular). Trouet et al teach the tri or tetrapeptide spacer arm is essential to obtain drug-protein conjugate that remain stable in serum from which the drug DNR be released intracellularly (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to link any drug such as daunorubicin to any targeting moiety as taught by Forsgren et al or Asai et al via a linking group such as tri or tetrapeptide linker as taught by Trouet et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the tri or tetrapeptide spacer arm is essential to obtain drug-protein conjugate that remains stable in serum from which the drug DNR be released intracellularly as taught by Trouet et al (see abstract, in particular).

Applicants' arguments filed 8/19/05 have been fully considered but are not found persuasive. Applicants' position is that methods for modulating biodistribution of a drug to an intracellular space in a host wherein both of drug moiety and the targeting moiety bind to intracellular proteins. In other words, the drug moiety and the targeting moiety bind to proteins that exist within a cell. Since Trouet et al has been cited for its disclosure of a linking group, it fails to make the deficiency of Forgren et al as detailed above. Forsgren discloses the binding characteristics of a rat protein that binds estramustine phosphate. The reference binding protein for estramustine is a secretory protein, not an intracellular protein target.

In response, Forsgren et al teach a method of targeting a drug to an intracellular site of a mammalian host such as male rat wherein the method comprises administering to the rat a bifunctional molecule such as Estracyt which consisting of a drug moiety such as nitrogen mustard linked to a targeting moiety such as estradiol-17 beta phosphate. The dephosphorylated metabolite of estracyt is estramustine that has affinity for its intracellular protein such as soluble estramustine binding protein of 10 to 30 x 10^{-9} M which is "at least" 10^{-6} M (see abstract, in particular). As evidence by the teachings of Asai et al that the estradiol moiety in the Estracyt

conjugate is useful as a carrier for selective distribution of the compound to the tissues (see abstract, in particular).

With respect to the argument that estramustine binding protein is a not an intracellular protein target, the estrmustine binding protein is a cytosolic protein that is located within cytoplasm of a cell (intracellular space) (see abstract of Forgren et al, in particular). Therefore, the reference cytosolic protein (estramustine binding protein) is still an intracellular protein since it is within cytoplasm of the cell.

11. Claims 16-18, 22-23, 30-34, 36 and 39-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forsgren et al (Cancer Res 39(12): 5155-64, Dec 1979; PTO 892) in view of WO 95/02684 (Jan 1995; PTO 1449).

Forsgren et al teach a method of targeting a drug to an intracellular site of a mammalian host such as male rat wherein the method comprises administering to the rat a bifunctional molecule such as Estracyt which consisting of a drug moiety such as nitrogen mustard linked to a targeting moiety such as estradiol-17 beta phosphate wherein said targeting moiety has affinity for its intracellular protein such as soluble estramustine binding protein of 10 to 30 x 10^{-9} M which is "at least" 10^{-4} M (see abstract, in particular). The reference bifunctional molecule exhibits a modulate biodistribution to the ventral prostate gland upon administration to a mammalian host (see abstract, in particular).

The claimed invention in claims 16 and 30 differs from the teachings of the reference only in that the method wherein the bifunctional molecule having a molecule weight that does not exceed about 5000 daltons consisting of a drug moiety optionally joined by a linking group to a targeting moiety wherein the targeting moiety has an affinity for its intracellular biodistribution modulating protein of at least about 10^{-4} M.

The claimed invention in claim 22 differs from the teachings of the reference only in that the method wherein the bifunctional molecule comprises a linking group.

The claimed invention in claims 32 differs from the teachings of the reference only in that the method wherein the mammalian host is a human.

The claimed invention in claims 39, 45 and 51 differs from the teachings of the reference only in that the method wherein the targeting moiety is a peptidyl-prolyl isomerase ligand.

The claimed invention in claims 40, 46 and 52 differs from the teachings of the reference only in that the method wherein the targeting peptidyl-prolyl isomerase ligand is a ligand for an FKBP or cyclophilin.

The claimed invention in claims 41, 47 and 53 differs from the teachings of the reference only in that the method wherein the targeting peptidyl-prolyl isomerase ligand is a ligand for an FKBP.

The claimed invention in claims 42, 48 and 54 differs from the teachings of the reference only in that the method wherein the targeting peptidyl-prolyl isomerase ligand is selected from the group consisting of FK506 and rapamycin.

The claimed invention in claims 43, 44, 49-50 and 55-56 differs from the teachings of the reference only in that the method wherein the targeting peptidyl-prolyl isomerase ligand is a ligand for cyclophilin.

The WO 95/02684 publication teaches a bifunctional molecule such as fusion protein comprising a targeting moiety such as various peptidyl-prolyl isomerase ligand linked to Fas (see page 14, lines 1-6, in particular) and method of making the same as a pharmaceutical for mammalian host such as human (see page 10, line 22-23, in particular). The reference targeting moiety such as peptidyl-prolyl isomerase ligand such as FK506 type ligand, cyclosporine (see page 4, lines 32-34, in particular), or rampamycin (see page 36, line 1, in particular) that binds to intracellular distribution molecule such as FKBP protein (see page 35, line 35-36, page 36, in particular) and has an affinity with a Kd value below about 10^{-6} M (see page 8, line 26, in particular) and preferably 2 and more orders of magnitude less than their kd (see page 8, line 32-34, in particular). The reference binding affinity of preferably 2 and more orders of magnitude less than their kd value below about 10^{-6} M includes the claimed at least 10^{-4} M (see page 35, line 32, in particular). The reference bifunctional molecule has a molecule weight that does not exceed about 5000 daltons (5 KD) (see page 4, line 12, claim 18 of WO 95/02684 publication, in particular). The reference bifunctional molecule includes a linking group (see page 37, line 5-23, in particular). The reference targeting moiety provides binding at the host target to a naturally occurring epitope to localize the concentration of the therapeutic product could be of great value (see page 44, line 2-10, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the estrogen targeting moiety as taught by Forsgren et al for the targeting moiety such as peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine and

rampamycin that has high affinity such as less than -6 M for its intracellular modulating protein such as FKBP as taught by the WO 95/02684 publication via a linker to a drug such as nitrogen mustard as taught by Forsgren et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the targeting moiety provides binding at the host target to a naturally occurring epitope to localize the concentration of the therapeutic product that could be of great value as taught by WO 95/02684 publication (see page 44, line 2-10, in particular). The use of ligand for FKBP or cyclophilin as a targeting moiety drug is an obvious variation of the reference teachings, especially in light of the teachings of the WO95/02684 that FK506 interacts with FKBP12 while cyclosporine A interacts with its intracellular receptor cyclophilin (page 40 lines 25-29) and the ligand has a size limitation of less than 5 kD (see page 4, line 13, page 33, lines 22-26, in particular).

Applicants' arguments filed 8/19/05 have been fully considered but are not found persuasive.

Applicants' position is that WO 95/02684 teaches large chimeric proteins that comprise a targeting domain and an action domain (see page 4, lines 22-30). The cited reference further teaches that the targeting domains such large chimeric protein are "capable of binding to FK-506-type ligand, a cyclosporine A type ligand, tetracyclic or steroid ligand" that are present in a cell and are referred to in the cited reference as oligomerization ligands (see page 4, lines 31-35, emphasized added). Therefore, the cited reference does not teach a moiety such as a peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine, and rapamycin as a targeting domain of a chimeric molecule, but instead teaches that such molecule can be targeted. In other words, the reference refers to receptors such FK506, and does not use ligands to those receptors for constructing bifunctional molecules (ligand plus drug) as claimed. For example, the cited reference provides in page 31, lines 1-3, that such a domain can be a FKRP and a cyclophilin receptor - not the ligand of such a receptor, is incorrectly stated in the Office Action. In addition, the cited reference further states that such a domain will be on the order of 25 kDa (see page 31, line 1%. The 5 kDa size limitation referred to in the Office Action actually refers to the ligands present in the cell. For example, the cited reference provides that such an oligomerization ligand is "preferably a non-protein and has a molecule weight of less than about 5 kDa" (see page 4, line 12). Therefore, contrary to the Office Action, the combined teaching of the cited references does

not provide for a bifunctional molecule comprising the nitrogen mustard domain of Forsgren et al. and a targeting domain having a molecular weight that does not exceed 5 kDa. Respectfully, the rejection appears to be based on an out-of-context reading of the references, based on hindsight from the present invention. The rejection appears to be based on an out of context reading of the references, based on hindsight from the present invention.

In response, the specification defines the Z moiety of the bifunctional ligands, e.g. FK506, rapamycin, cyclosporine A, and the like (see page 21, lines 3-5 of specification). The specification discloses FK506 is covalently attached to the linker or drug moiety and the endogenous biodistribution modulating is either an FKBP or a cyclophilin (see page 26).

The WO 95/02684 publication teaches a bifunctional molecule such as fusion protein comprising a targeting moiety such as various peptidyl-prolyl isomerase ligand linked to Fas (see page 14, lines 1-6, in particular) and method of making the same as a pharmaceutical for mammalian host such as human (see page 10, line 22-23, in particular). The reference targeting moiety is peptidyl-prolyl isomerase ligand such as FK506, cyclosporine (see page 4, lines 32-34, in particular), or rampamycin (see page 36, line 1, in particular) that binds to intracellular distribution molecule such as FKBP protein (see page 35, line 35-36, page 36, in particular) and has high affinity with a Kd value below about 10^{-6} M (see page 8, line 26, in particular) and preferably 2 and more orders of magnitude less than their kd (see page 8, line 32-34, in particular). The reference targeting domain such as FK506, cyclosporine and rampamycin is the same targeting domain FK506, rapamycin, cyclosporine A, and the like as defined by instant specification (see page 21, lines 3-5 of specification). The WO95/02684 publication further teaches the binding partner of FKBP12 such as FK506, which is the ligand (see page 85, line 18, in particular) as well as the binding partner of cyclosporine A such as cyclophilin (see page 40, line 25-30, in particular). The WO95/02684 publication further teaches the use of FKBP12 as the targeting domain FKBP12 linked to drug such as Fas (see page 57, col. 24-28, in particular). The use of the binding partner of FKBP or cyclophilin, in this case, the ligand FK506 and cyclosporine, respectively, as a targeting moiety to target drug is an obvious variation of the reference teachings, especially in light of the teachings of the WO95/02684 that FK506 interacts with FKBP12 while cyclosporine A interacts with its intracellular receptor cyclophilin (page 40 lines 25-29) and the ligand has a size limitation of less than 5 kD (see page 4, line 13, page 33, lines 22-26, in particular). In fact, the WO95/02684 publication also teaches FK506 (targeting moiety) capable of binding to receptor domain, i.e. FKBP (see page 35, line 24, in particular)

linked to a drug moiety such as cyclosporine A (see page 77, line 15, in particular). Given the molecular weight of the FK506 is 822.05 Dalton and the molecular weight of cyclosporine A is 1203 Dalton, the sum of the two molecular weight is 2025.05 Dalton, which is less than the claimed limitation of not exceed about 5000 dalton or 5kD.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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